

## REMARKS

By this amendment, minor amendments have been made to Claims 14, 17-19 and 25. Following entrance of this amendment, Claims 1 and 4-25 remain pending in the application. For the reasons as stated below, and in the attached Declaration of Dr. Jeanne-Marie Lecomte, Ph.D. (“Declaration”), the application in its present form overcomes all prior rejections and is in condition for immediate allowance.

In the Official Action, the Examiner rejected Claims 14-19 and 25 under 35 U.S.C. §112 on the grounds that the dependent claims utilized “open” language wherein the independent claim on which they directly or indirectly depend used the “consisting essentially of” language. Without addressing the merits of this rejection, which Applicants contest, the claims have been amended in an effort to expedite the allowance of the application, and these amendments make the Examiner’s rejection moot.

In the Official Action, the Examiner rejected Claims 1 and 5-25 under the written description requirement of 35 U.S.C. §112 on the grounds that the disclosure did not “set forth the novel and unobvious character of the instant invention” and thus failed to define what was excluded by the “consisting essentially of” language in the claims. This rejection, insofar as applied to the claims as amended, is respectfully traversed.

As an initial matter, it is well established that the term “consisting essentially of:” allows for the inclusion of additional elements to the claim which do not affect the “basic and material characteristics” of the claim. As set forth in MPEP 2111.03, “By using the term ‘consisting essentially of,’ the drafter signals that the invention necessarily includes the listed ingredients and is open to **unlisted** ingredients that do not materially affect the

basic and novel properties of the invention.” (Citing *Ex parte Davis*, 80 USPQ 448 at 450 (Pat. Off. Bd. App. 1948) (Emphasis added). Accordingly, in the first place, the Examiner did not recite the correct standard in determining whether the specification supports the use of the “consisting essentially of” language which is set forth in MPEP §2163, II.A.1..

Moreover, the specification makes it entirely clear what the basic and novel properties of the claimed invention are, namely the ability of Applicants’ novel and unobvious combinations to achieve an anti-diarrheal effect while administering this combination to patients suffering from diarrhea. This is disclosed throughout the specification, e.g., page 2, lines 9-19, page 3, lines 9-14 and elsewhere. Accordingly, the claims exclude those compositions wherein added ingredients would eliminate the anti-diarrheal effect. Even further, the specification repeatedly recites that non-active ingredients that can be added to the combination in addition to the active ingredients, see e.g., page 8, bottom, page 11, top and elsewhere.

Accordingly, the claims including the “consisting essentially of” language are fully supported in the specification, and the Examiner’s rejections on the basis of the written description requirement are respectfully traversed and should be withdrawn.

In the Official Action, the Examiner rejected Claims 1 and 5-25 under 35 U.S.C. §103(a) as obvious over the Cojocarú et al. article (“Cojocarú”) in view of the Cubeddu et al. article (“Cubeddu”) and the Boige et al. article (“Boige”). This rejection, insofar as applied to the claims as amended, is respectfully traversed for the reasons that follow.

Contrary to the position of the Examiner, Cojocaru merely discloses the benefits of racecadotril administration for acute diarrhea treatment: rehydration, lower number of stools and faster recovery. This document does not mention the combination of racecadotril with any antiemetic agent, and is silent about ondansetron or granisetron. This document would certainly not teach one skilled in the art that it would be possible to combine an antiemetic agent with racecadotril and merely reflects the general state of the art prior to the present invention.

In addition, it is well known clinically that ondansetron is an anti-emetic agent (i.e. inhibiting nausea) and does **not** possess anti-diarrheal activity. Rather, **to the contrary**, it was found that ondansetron alone **increases** the occurrence of diarrheal episodes. This fact was shown in the Cubeddu reference cited by the Examiner which relates to the administration of ondansetron for the treatment of emesis associated with acute gastroenteritis. Cubeddu shows that the administration of ondansetron actually **increases** the number of diarrheal episodes when compared to a placebo (see Table 3, p.189 of Cubeddu). In particular, Cubeddu concludes (p. 187, last paragraph) that “compared with placebo, significantly more episodes of diarrhea were reported in the ondansetron (P=0.013 group.” See Declaration, ¶ 8.

Based on the teaching of Cubeddu, one skilled in the art would be **taught away** from using ondansetron in any combination where **anti-diarrheal** effects were desired. The cited Cubeddu reference **teaches away** from the present claims because it would have led the person skilled in the art **away** from making the combination of the invention.

The final reference cited by the Examiner, Boige, also does not disclose or suggest the present claims nor can it be combined with any of the other references to make the claimed invention obvious. Boige merely describes the administration of ondansetron to treat emesis and the administration of racecadotril to treat diarrhea. Boige **never** discloses or suggests in any manner combining these substances to suppress the side effect of racecadotril and thereby potentiate the anti-diarrheal effect of the latter.. See Declaration, ¶ 7.

Thus, none of the references cited by the Examiner, either singly or in combination, disclose or suggest the present invention. Moreover, in light of the disclosure of Cubeddu showing that ondansetron alone **increased** the occurrence of diarrhea, one seeking to treat acute diarrhoea would have been **taught away** from combining ondansetron or granisetron with racecadotril or dexecadotril as in the case in Applicants' claims.

Since the references cited by the Examiner thus do not teach or suggest the present invention, and indeed **teach away** from the present invention, Applicants submit that on this basis alone, the Examiner's rejection on the basis of the cited references is respectfully traversed and should be withdrawn.

However, even further, as set forth in the attached Declaration of Dr. Lecomte, Ph.D., additional clinical data has now been provided which shows that the present invention provides surprising synergy and unexpected beneficial results which further evidences the non-obviousness of the present claims.

In this study, the co-administration of ondansetron with dexecadotril was shown to provide synergy and to surprisingly suppress the increase in the intestinal transit induced by dexecadotril while reducing the number of diarrheic stools and the duration of diarrhea. Diarrhea generally involves two components, namely loss of water and salts and acceleration of the intestinal tract. Loss of water and salts can lead to dehydration which is one of the main life-threatening complications of diarrhea. Racecadotril and dexecadotril exhibit strong anti-secretory effects but also increase an acceleration of the intestinal tract which is an undesirable side effect. Declaration, ¶¶ 4-6.

Previously, Applicants had shown that co-administration of racecadotril with granisetron surprisingly suppresses this side effect and thus potentiates the anti-diarrheal effect. Applicants have thus previously shown that the undesirable side effect of racecadotril is thus prevented by the addition of granisetron in accordance with Applicants' invention, and there was certainly no disclosure or suggestion in the prior art that granisetron would slow down the increase of intestinal transit caused by racecadotril. Declaration, ¶ 6.

Even further, the attached Declaration shows that co-administration of ondansetron with dexecadotril also surprisingly suppresses the increase in intestinal transit time induced by dexecadotril while reducing the number of diarrheic stools and the duration of diarrhea. Declaration, ¶¶ 9, 9.1, 9.2

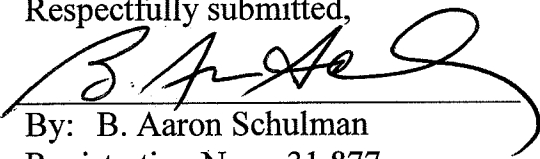
Given that ondansetron does not possess anti-diarrheal activity and even increases diarrhea when used alone, the above potentialization of the anti-diarrheal activity of dexecadotril when combined with ondansetron illustrates a synergy between these two compounds. These beneficial results are thus surprising and would not have been expected by one skilled in the art. Declaration ¶ 10.

Applicant thus submits that the secondary considerations as evidenced in the attached Declaration only further support the non-obviousness of the present claims, and provide even further grounds to show that the Examiner's rejection on the basis of obviousness is improper and should be withdrawn.

In light of the arguments and amendments as set forth above, Applicants submit the present application overcomes all prior rejections and has been placed in condition for immediate allowance. Such action is respectfully requested.

Respectfully submitted,

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